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(54) Title
9-HALOGEN-11BETA -HYDROXY PROSTAGLANDIN DERIVATIVE, PROCESS FOR PRODUCING IT AND ITS USE AS A MEDICAMENT

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(56) Prior Art Documents
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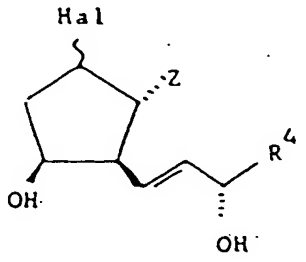
AU 543797 65190/80 C07C 405/00
AU 624078 20785/88 C07C 405/00

(57) The active ingredients according to the invention show a cytoprotective and ulcer-healing effect, inhibit the gastric acid secretion and thus counteract the undesirable effects of nonsteroidal anti-inflammatory substances. They further have a cytoprotective effect on the liver, kidneys and also on the pancreas.

CLAIM

1. 9-Halogen-11β-hydroxy-prostane derivatives of formula I



(I),

in which Z means the radicals

.../2

Hal means an α- or β-position chlorine or fluorine atom,

R^1 means the radical CH_2OH or $-C(=O)-OR^2$

with R^2 meaning a hydrogen atom, an alkyl, cycloalkyl, aryl or heterocyclic radical or R^1 means the radical $-C(=O)-NHR^3$ with R^3 meaning an acid radical or radical R^2 and R^4 means a cycloalkyl group, and if R^2 has the meaning of a hydrogen atom, its salts with physiologically compatible bases and its cyclodextrin clathrates.

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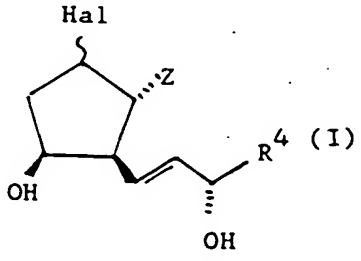
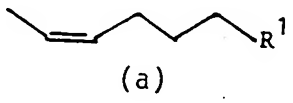
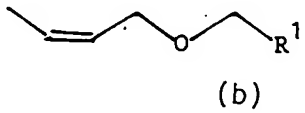
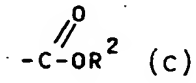
(54) Title: 9-HALOGEN-11β-HYDROXY PROSTAGLANDIN DERIVATIVE, PROCESS FOR PRODUCING IT AND ITS USE AS A MEDICAMENT

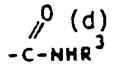
(54) Bezeichnung: 9-HALOGEN-11β-HYDROXY-PROSTAGLANDINDERIVATE, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE VERWENDUNG ALS ARZNEIMITTEL











(57) Abstract

The invention relates to 9-halogen-11β-hydroxy prostaglandin derivatives of formula (I) in which Z is the radical (a) or (b), Hal is an α or β-fixed chlorine or fluorine atom, R^1 is the radical CH_2OH or (c), R^2 is a hydrogen atom, an alkyl, cycloalkyl, aryl or heterocyclic radical or R^1 is the radical (d), where R^3 is an acid radical or the radical R^2 and R^4 is a cycloalkyl group, and if R^2 is a hydrogen atom, their salts with physiological acceptable bases and their cyclodextrin clathrates, process for producing them and their pharmaceutical use.

(57) Zusammenfassung

Die Erfindung betrifft 9-Halogen-11β-hydroxy-prostanderivate der Formel (I), worin Z die Reste (a) oder (b), Hal ein α- oder β-ständiges Chlor- oder Fluoratom, R^1 den Rest CH_2OH oder (c) mit R^2 in der Bedeutung eines Wasserstoffatoms, eines Alkyl-, Cycloalkyl-, Aryl- oder heterocyclischen Restes oder R^1 den Rest (d) mit R^3 in der Bedeutung eines Säurerestes oder des Restes R^2 und R^4 eine Cycloalkylgruppe, und falls R^2 die Bedeutung eines Wasserstoffatoms hat, deren Salze mit physiologisch verträglichen Basen bedeuten und deren Cyclodextrinclathrate, Verfahren zu ihrer Herstellung und ihre pharmazeutische Verwendung.

9-Halogen-11β-hydroxy-prostaglandin Derivatives, Process for their Production and their Use as Pharmaceutical Agents

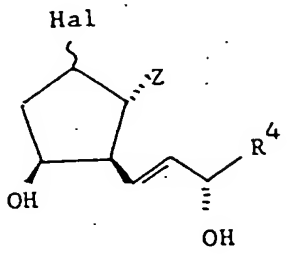
Object of this invention are new 9-halogen-11β-hydroxy-prostaglandin derivatives, process for their production as well as their use as pharmaceutical agents.

It is known from the very extensive prior art of the prostaglandins and their analogs that this family of compounds, because of its biological and pharmacological properties, is suitable for treatment of mammals, including humans, but its use as pharmaceutical agents often encounters difficulties. Most natural prostaglandins have a duration of action too short for therapeutic purposes, since they are metabolically catabolized too quickly by various enzymatic processes. The purpose of all structural changes is to increase the duration of action as well as the selectivity of the activity.

It has now been found that the new 9-halogen-11β-hydroxy-prostaglandin derivatives have an excellent action specificity, better effectiveness, longer duration of action than natural prostaglandins and their derivatives and are suitable especially for oral administration.

The invention relates to 9-halogen-11β-hydroxy-prostane

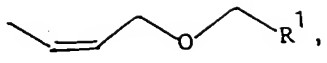
derivatives of formula I



(I),

in which Z means the radicals

or



Hal means an α- or β-position chlorine or fluorine atom,

R^1 means the radical CH_2OH or $-C(=O)-OR^2$ with R^2 meaning a hydrogen atom, an alkyl, cycloalkyl, aryl or heterocyclic radical or R^1 means the radical $-C(=O)-NHR^3$ with R^3 meaning an acid radical or radical R^2 and R^4 means a cycloalkyl group, and if R^2 has the meaning of a hydrogen atom, its salts with physiologically compatible bases and its cyclodextrin clathrates.

As alkyl groups R^2, straight or branched alkyl groups with 1-10 C atoms are to be considered, such as, for example, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl, heptyl, decyl. Alkyl groups R^2 can optionally be substituted once to several times by halogen atoms, alkoxy groups, optionally substituted aryl or aroyl groups, dialkylamino and trialkylammonium, and the single substitution is to be

preferred. As substituents, there can be mentioned, for example, fluorine, chlorine or bromine, phenyl, dimethylamino, diethylamino, methoxy, ethoxy. As preferred alkyl groups R^2, those with 1-4 C atoms, such as, e.g., methyl, ethyl, propyl, dimethylaminopropyl, isobutyl, butyl, can be mentioned.

As aryl groups R^2, both substituted and unsubstituted aryl groups are suitable, such as, for example, phenyl, 1-naphthyl and 2-naphthyl, which can be substituted respectively by 1-3 halogen atoms, a phenyl group, 1-3 alkyl groups with respectively 1-4 C atoms, a chloromethyl, fluoromethyl, trifluoromethyl, carboxyl, hydroxy or alkoxy group with 1-4 C atoms. Preferred are the substituents in 3-and 4-position on the phenyl ring, for example, by fluorine, chlorine, alkoxy or trifluoromethyl or in 4-position by hydroxy.

Cycloalkyl group R^2 can contain 3-10, preferably 5 and 6 carbon atoms in the ring. The rings can be substituted by alkyl groups with 1-4 carbon atoms. For example, cyclopentyl, cyclohexyl, methylcyclohexyl and adamantyl can be mentioned.

As heterocyclic groups R^2, 5- and 6-membered heterocycles are suitable, which contain at least 1 heteroatom, preferably nitrogen, oxygen or sulfur. For example, there can be mentioned 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, oxazolyl, thiazolyl, pyrimidinyl, pyridazinyl, pyrazinyl, 3-furyl, 3-thienyl, 2-tetrazolyl i.a.

As acid radical R^3, physiologically compatible acid radicals are suitable. As acids, organic carboxylic acids and sulfonic acids with 1-15 carbon atoms are suitable, which belong to the

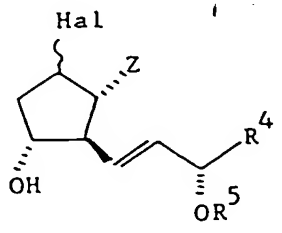
aliphatic, cycloaliphatic, aromatic, aromatic-aliphatic and heterocyclic series. These acids can be saturated, unsaturated and/or polybasic and/or substituted in the usual way. As examples for substituents, alkyl, hydroxy, alkoxy, oxo or amino groups or halogen atoms can be mentioned. For example, the following carboxylic acids can be mentioned: formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, trimethylacetic acid, diethylacetic acid, tert-butylacetic acid, cyclopropylacetic acid, cyclopentylacetic acid, cyclohexylacetic acid, cyclopropanecarboxylic acid, cyclohexanecarboxylic acid, phenylacetic acid, phenoxyacetic acid, methoxyacetic acid, ethoxyacetic acid, monochloroacetic acid, dichloroacetic acid and trichloroacetic acid, aminoacetic acid, diethylaminoacetic acid, piperidinoacetic acid, morpholinoacetic acid, lactic acid, succinic acid, adipic acid, benzoic acid, benzoic acids substituted with halogen, trifluoromethyl, hydroxy, alkoxy or carboxy groups, nicotinic acid, isonicotinic acid, furan-2-carboxylic acid, cyclopentylpropionic acid. As preferred acyl radicals, those with up to 10 carbon atoms are considered. As sulfonic acids, for example, alkanesulfonic acids with 1-10 C atoms, such as, e.g., methanesulfonic acid, ethanesulfonic acid, isopropanesulfonic acid and butanesulfonic acid as well as β-chloroethanesulfonic acid, cyclopentanesulfonic acid, cyclohexanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic

acid, p-chlorobenzenesulfonic acid, N,N-dimethylaminosulfonic acid, N,N-diethylaminosulfonic acid, N,N-bis-(β-chloroethyl)-aminosulfonic acid, N,N-diisobutylaminosulfonic acid, N,N-dibutylaminosulfonic acid, pyrrolidino, piperidino, piperazino, N-methylpiperazino and morpholinosulfonic acid are suitable. Acyl radicals or alkanesulfonic acid radicals with 1-4 C atoms are especially preferred.

Cycloalkyl group R^4 can contain 3-10, preferably 3-6 carbon atoms, in the ring. The rings can be substituted by alkyl groups with 1-4 carbon atoms. For example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methyl-cyclohexyl, especially 4-methylcyclohexyl, 4-ethylcyclohexyl, 4-propylcyclohexyl and adamantyl can be mentioned.

For salt formation, inorganic and organic bases are suitable, as they are known to one skilled in the art for the formation of physiologically compatible salts. For example, there can be mentioned alkali hydroxides, such as sodium and potassium hydroxide, alkaline-earth hydroxides, such as calcium hydroxide, ammonia, amines, such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, tris-(hydroxymethyl)-methylamine, etc.

The invention further relates to a process for the production of 9-halogen-11β-hydroxy-prostane derivatives of formula I according to the invention, characterized in that in a way known in the art, a compound of formula II



(II),

in which Z, Hal and R^4 have the meanings already stated above and R^5 can be a silyl radical, for example, there can be mentioned trimethylsilyl, dimethyltert-butylsilyl, dimethyl-hexylsilyl, diphenyl-tert-butylsilyl and tribenzylsilyl, is intermediately converted to a ketone by an oxidation with chromic acid or a chromic acid derivative, the latter then is reacted by a reduction in a mixture of epimeric alcohols and after purification, protecting groups optionally present in any sequence are cleaved and/or an

esterified carboxyl group (R^1=-C-OR^2) is saponified and/or reduced.

The reaction of compounds of formula II to compounds of formula I takes place first by the oxidation of the free hydroxy group according to the methods known to one skilled in the art. As an oxidizing agent, there can be used, for example: Jones reagent (J. Chem. Soc. 1953, 2555), pyridinium dichromate (Tetrahedron Letters 1979, 399), Collins reagent (Tetrahedron Letters 1968, 3363), pyridinium chlorochromate (Tetrahedron Letters 1975, 2647), the method with pyridinium chlorochromate is preferred.

The oxidation with Jones reagent is performed at temperatures of -40°C to +40°C, preferably -20°C to 10°C in acetone as solvent. The oxidation with pyridinium dichromate is performed at temperatures of 0°C to 100°C, preferably 20°C to 40°C in a solvent inert toward the oxidizing agent, for example, dimethylformamide.

The oxidation with Collins reagent or pyridinium chlorochromate is performed at temperatures of -20°C to 50°C, preferably 0°C to 25°C in methylene chloride as solvent.

The subsequent reduction is performed according to the methods known to one skilled in the art, in which the previously obtained ketone is preferably reacted with sodium borohydride at temperatures between -40°C and +40°C, preferably -30°C to 0°C in a mixture of methanol and tetrahydrofuran.

After chromatographic separation of the epimeric alcohols, the release of the functionally modified hydroxy group takes place according to known methods.

For example, the cleavage of the silyl protecting group is performed by an organic acid, such as, for example, oxalic acid, acetic acid in a water-miscible organic solvent, such as, e.g., tetrahydrofuran or by a fluoride compound, such as, for example, tetrabutylammonium fluoride, cesium fluoride, pyridine-HF complex in an organic solvent, such as, e.g., tetrahydrofuran, dioxane.

If Z is to mean $R^1=-\overset{\overset{O}{\parallel}}{C}-OR^2$ with $R^2=H$, a saponification takes place according to the methods known to one skilled in the art by conversion with an alkali or alkaline-earth hydroxide in an aqueous solution of an alcohol. As alcohols, aliphatic alcohols are suitable, such as, e.g., methanol, ethanol, butanol, etc., preferably methanol. As alkali hydroxides, potassium, sodium and lithium salts can be mentioned. Potassium and lithium salts are preferred. As alkaline-earth hydroxides, for example, calcium

hydroxide is suitable. The reaction takes place at -10°C to +70°C, preferably at +25°C.

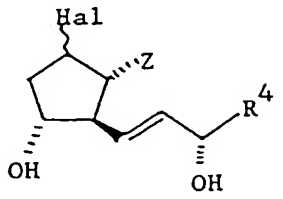
The reduction to the compounds of formula I with R^1 meaning a $-CH_2OH$ group is performed with a reducing agent suitable for the reduction of esters or carboxylic acids, such as, for example, lithium aluminum hydride, diisobutyl aluminum hydride, etc. As solvent, diethyl ether, tetrahydrofuran, dimethoxyethane, toluene, etc., are suitable. The reduction is performed at temperatures of -30°C up to boiling temperature of the solvent used, preferably 0°C to 30°C.

The prostaglandin derivatives of formula I with R^2 meaning a hydrogen atom can be converted to a salt with suitable amounts of the corresponding inorganic base with neutralization. For example, by dissolving the corresponding PG acids in water, which contains the stoichiometric amount of the base, the solid inorganic salt is obtained after evaporating the water or after adding a water-miscible solvent, e.g., alcohol or acetone.

For the production of an amine salt, which takes place in the usual way, the PG acid is dissolved, e.g., in a suitable solvent, for example, ethanol, acetone, diethyl ether, acetonitrile or benzene and at least the stoichiometric amount of the amine is added to this solution. In this way, the salt is obtained usually in solid form or is isolated in the usual way after evaporation of the solvent.

The compounds of formula II being used as initial material can be produced, for example, with a 15-silyl-protected α-hydroxy

group, by converting in a way known in the art a diol of formula III, known according to EP 30377, EP 69696 and DE 3724190 or to be synthesized analogously,

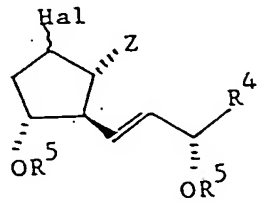


(III),

in which Z (if R^1 =-C(=O)-OR^2 with R^2=H), Hal and R^4 have the meanings already indicated above, by reaction with a silyl compound of formula IV,

R^5Cl (IV),

in which R^5 has the meaning already indicated above, to the compounds of formula V.



(V),

By a subsequent selective silyl ether cleavage in the 11-position, the compounds of formula II being used as initial material are obtained with a 15-silyl-protected α-hydroxy group.

The new prostaglandin analogs of formula I are valuable pharmaceutical agents, since in a similar spectrum of activity, they exhibit a significantly improved (higher specificity) and

above all, significantly longer activity than the corresponding natural prostaglandins. Moreover, the natural prostaglandin-D_2 is reacted to the vessel-active 9α,11β-PGF_2.

The 9-halogen-11β-hydroxyprostaglandin derivatives of formula I according to the invention are distinguished by PGD_2-typical properties, i.e., they bind well to the PGD_2 receptor.

The active ingredients according to the invention show a cytoprotective and ulcer-healing effect, inhibit the gastric acid secretion and thus counteract the undesirable effects of nonsteroidal anti-inflammatory substances. They further have a cytoprotective effect on the liver, kidneys and also on the pancreas.

Several of the compounds have an antihypertensive effect and inhibit the platelet aggregation, moreover, they have regulating influences on the cardiac rhythm. Possibilities of use in circulatory disturbances of cerebral, coronary and peripheral type, in myocardial infarction or cerebral hemorrhage and cerebral edemas result from the above. Also, the migraine is platelet-caused in its symptoms and signs and thus an important indication.

Further, the compounds are suitable for glaucoma treatment.

Because of the inhibiting effect of leukocytes, which several of the compounds show, and their blocking action on the release of oxygen radicals, the substances are suitable to calm excess inflammatory reactions of the cellular immunological response, for example, in reperfusion or in diseases of the rheumatic type.

The new prostaglandins can also be used in combination, e.g., with β-blockers, diuretics, phosphodiesterase inhibitors, calcium antagonists, thromboxane antagonists, thromboxane synthetase and cyclooxygenase inhibitors, anticoagulant substances, such as also fibrinolytic agents, leukotriene antagonists, leukotriene synthetase inhibitors and antiprogesterones.

Those prostaglandin analogs which have a high affinity for receptors in membrane preparations of brain can, because of their properties, be used to influence mental processes, such as, e.g., sleep.

The dose of the compounds is 1-1500 μg/kg/day, if they are administered to human patients.

For medical use, the active ingredients can be converted to a form suitable for inhalation, for oral, parenteral or topical (e.g., vaginal) administration. For inhalation, aerosol solutions are suitably produced.

For oral administration, for example, tablets, coated tablets or capsules are suitable.

For parenteral administration, sterile, injectable, aqueous or oily solutions are used.

For vaginal administration, e.g., suppositories are suitable and usual.

The invention thus relates also to pharmaceutical agents based on compounds of formula I and usual auxiliary agents and vehicles, including cyclodextrin clathrates.

The active ingredients according to the invention are to be used in connection with the auxiliary agents known and usual in galenicals, e.g., for the production of preparations for treatment of hypertension or for treatment of gastrointestinal disturbances, such as, e.g., for healing of gastric and duodenal ulcers. For this purpose but also for other uses, the preparations can contain 0.01-100 mg of the active compound.

The following examples are to explain the invention in more detail, without a limitation thus being made.

Example 1

(5Z,13E)-(9R,11S,15S)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester

4.0 g of pyridinium chlorochromate is added to a solution of 360 mg of (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11-hydroxy-15-tert-butyldimethylsilyloxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid ethyl ester in 150 ml of methylene chloride at 0°C under argon and then allowed to stir for 3 hours at 25°C. Then, it is mixed with Celite, filtered, rewashed well with methylene chloride and concentrated by evaporation in a vacuum. 355 mg of (5Z,13E)-(9R,11S,15S)-9-chloro-15-cyclohexyl-11-oxo-15-tert-butyldimethylsilyloxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester is obtained as oil.

IR ($CHCl_3$): 3000, 2955, 2930, 2858, 1747, 1735, 1250, 970, 838 cm^{-1}.

The ketone produced above is dissolved under argon in 15 ml of methanol/tetrahydrofuran (2+1) and 200 mg of sodium borohydride is added at -30°C. After 30 minutes of stirring at -30°C, it is mixed with a little glacial acetic acid and concentrated by evaporation in a vacuum. The residue is taken up in water, extracted three times with methylene chloride, the combined organic phases are washed with brine, dried on sodium sulfate and, after the filtration, concentrated by evaporation in a vacuum. The thus obtained crude product is chromatographed on silica gel. With hexane/10-20% ethyl acetate, besides the polar 11-α-epimeric alcohol, 94 mg of the nonpolar (5Z,13E)-(9R,11S,15S)-9-chloro-15-cyclohexyl-11-hydroxy-15-tert-

butyldimethylsilyloxy-16,17,18,18,19-pentanor-5,13-prostadienoic acid methyl ester is obtained as colorless oil.

IR ($CHCl_3$): 3610, 3500, 3000, 2955, 2930, 2855, 1733, 1250, 975, 848 cm^{-1}.

The above-produced 11β-alcohol is heated in a mixture of acetic acid/water/tetrahydrofuran (65+35+10) for 6 hours to 40°C and then further stirred for 14 hours at 24°C. With adding toluene, it is concentrated by evaporation in a vacuum and the thus obtained residue is chromatographed on silica gel. With hexane/0-80% ethyl acetate, 55 mg of the title compound is obtained as colorless oil.

IR ($CHCl_3$): 3605, 3430, 3000, 2950, 2928, 2858, 1730, 978 cm^{-1}.

The 15-homosilylether used as initial material is obtained as follows:

1a) <u>(5Z,13E)-(9R,11R,15S)-9-Chloro-15-cyclohexyl-11,15-bis-tert-butyl-dimethylsilyloxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester</u>

1 g of imidazole and 1.1 g of tert-butyldimethylsilyl chloride are added to a solution of 600 mg of (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester in 10 ml of dimethylformamide at 0°C under argon and stirred for 24 hours at 25°C. Then, the reaction solution is added to water and extracted several times with hexane/ether (1+1). The combined organic phases are washed once with water, dried on magnesium sulfate, filtered and concentrated by evaporation in a vacuum.

The thus obtained crude product is purified by chromatography on silica gel. With hexane/0-10% ethyl acetate, 584 mg of the title compound is obtained as colorless oil.

IR ($CHCl_3$): 3000, 2952, 2930, 2858, 1730, 1250, 975, 848 cm^{-1}.

1b) (5Z,13E)-(9R,11R,15S)-9-Chloro-15-cyclohexyl-11-hydroxy-15-tert-butyl-dimethylsilyloxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester

20 ml of a 1-molar solution of tetrabutylammonium fluoride in tetrahydrofuran is added to a solution of 580 mg of the above-produced bis-silyl-ether in 5 ml of tetrahydrofuran at 25°C under argon and stirred for 30 minutes at 25°C. Then, it is diluted with 100 ml of ether, washed three times with water, dried on sodium sulfate and, after filtration, concentrated by evaporation in a vacuum. The thus obtained residue is chromatographed on silica gel. With hexane/0-10% ethyl acetate, 382 mg of the title compound is obtained as colorless oil.

IR ($CHCl_3$): 3605, 3520, 3000, 2955, 2930, 2858, 1732, 1252, 975, 848 cm^{-1}.

Example 2

(5Z,13E)-(9R,11S,15S)-9-Chloro-15-cyclohexyl-11,15-hydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid-tert-butyl ester

Analogously to example 1, 98 mg of the title compound is obtained as colorless oil from 360 mg of (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11-hydroxy-3-oxa-15-bis-tert-butyldimethylsilyloxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid-tert-butyl ester.

IR ($CHCl_3$): 3600, 3415, 3200, 2988, 2930, 2858, 1742, 1238, 982 cm^{-1}.

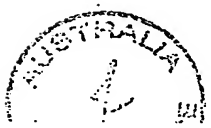
The initial material for the production of the title compound is obtained according to example 1a,b) from 500 mg of (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid-tert-butyl ester.

Example 3

(5Z,13E)-(9R,11S,15S)-9-Fluoro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester

Analogously to example 1, 210 mg of the title compound is obtained as colorless oil from 1.03 g of (5Z,13E)-(9R,11R,15S)-9-fluoro-15-cyclohexyl-11-hydroxy-15-tert-butyldimethylsilyloxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester.

IR ($CHCl_3$): 3645, 3605, 3420, 3000, 2950, 2925, 2855, 1730, 1245, 975 cm^{-1}.



The initial material for the production of the title compound is obtained according to example 1a,b) from 1.48 g of (5Z,13E)-(9R,11R,15S)-9-fluoro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid methyl ester.

Example 4

(5Z,13E)-(9R,11S,15S)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid

52 mg of the ester produced according to example 1 is stirred in 4 ml of a mixture of potassium hydroxide in ethanol/water (2 g of KOH in 100 ml of EtoH/H_2O 3+1) for 4 hours at 25°C. Then, it is acidified with diluted hydrochloric acid to pH = 5, extracted several times with ethyl acetate, the combined organic phases are washed with brine, dried on sodium sulfate and, after filtration, concentrated by evaporation in a vacuum. The thus obtained residue is chromatographed on silica gel. With methylene chloride/0-70% acetone, 33 mg of the title compound is obtained as colorless oil.

IR ($CHCl_3$): 3600, 3400, 3000, 2950, 2928, 2855, 1712, 978 cm^{-1}.

Example 5

(5Z,13E)-(9R,11S,15S)-9-Chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid

95 mg of the ester produced according to example 2 dissolved in 0.85 ml of methanol is mixed with 10.3 mg of lithium hydroxide dissolved in 0.85 ml of water and stirred for 18 hours at 25°C.

Then, it is acidified with diluted hydrochloric acid until pH = 5, extracted several times with ethyl acetate, the combined organic bases are washed with brine, dried on sodium sulfate and, after filtration, concentrated by evaporation in a vacuum. The thus obtained residue is chromatographed on silica gel. With hexane/70% ethyl acetate/0-5% 2-propanol, 81 mg of the title compound is obtained as colorless oil.

IR (Film): 3420, 3020, 2970, 2925, 2850, 1732, 978 cm^{-1}.

Example 6

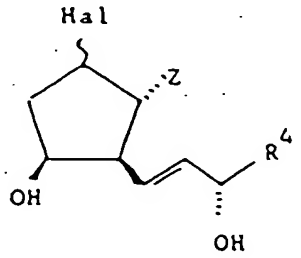
(5Z,13E)-(9R,11R,15S)-9-Fluoro-15-cyclohexyl-11,15-dihydroxy-16,17,18,19,20-pentanor-5,13-prostadienoic acid

Analogously to example 4, 91 mg of the title compound is obtained as colorless oil from 204 mg of the ester produced according to example 3.

IR ($CHCl_3$): 3680, 3600, 3420, 3030, 3000, 2960, 2925, 2855, 1710, 976 cm^{-1}.

The claims defining the invention are as follows:

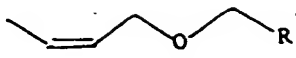
1. 9-Halogen-11β-hydroxy-prostane derivatives of formula I



(I),

in which Z means the radicals

or

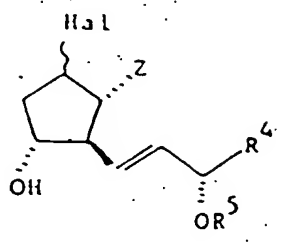


Hal means an α- or β-position chlorine or fluorine atom,

R^1 means the radical CH_2OH or $-C(=O)-OR^2$

with R^2 meaning a hydrogen atom, an alkyl, cycloalkyl, aryl or heterocyclic radical or R^1 means the radical $-C(=O)-NHR^3$ with R^3 meaning an acid radical or radical R^2 and R^4 means a cycloalkyl group, and if R^2 has the meaning of a hydrogen atom, its salts with physiologically compatible bases and its cyclodextrin clathrates.

2. Process for the production of 9-halogen-11β-hydroxy-prostane derivatives of formula I, as defined in claim 1, according to the invention, characterized in that, in a way known in the art, a compound of formula II



(II),

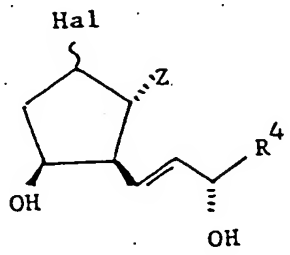
in which Z, Hal and R^4 have the meanings already indicated above and R^5 can be a silyl radical, is intermediately converted to a ketone by oxidation with chromic acid or a chromic acid derivative, the latter then is reacted by reduction in a mixture of epimeric alcohols and protecting groups optionally present in any sequence are cleaved and/or an

esterified carboxyl group (R^1=-C(=O)-OR^2) is saponified and/or reduced.

3. Pharmaceutical agents, containing one or more compounds of formula I, as defined in claim 1, and usual auxiliary agents and vehicles.

Abstract

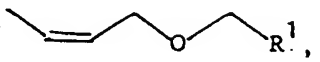
The invention relates to 9-halogen-11β-hydroxy-prostane derivatives of formula I



(I),

in which Z means the radicals

or



Hal means an α- or β-position chlorine or fluorine atom,

R^1 means the radical CH_2OH or $-C(=O)-OR^2$ with R^2 meaning a hydrogen atom, an alkyl, cycloalkyl, aryl or heterocyclic radical or R^1 means the radical $-C(=O)-NHR^3$ with R^3 meaning an acid radical or radical R^2 and R^4 means a cycloalkyl group, and if R^2 has the meaning of a hydrogen atom, its salts with physiologically compatible bases and its cyclodextrin clathrates, process for their production and their pharmaceutical use.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DE 91/00881

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5]: C 07 C 405/00 // A 61 K 31/557

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	WO, A, 8903384 (PHARMACIA AB) 20 April 1989 see claims	1-3
Y	EP, A, 0030377 (SCHERING) 10 December 1979 see claims (cited in the application)	1-3
Y	EP, A, 0299914 (SCHERING) 18 January 1989 see claims (cited in the application) & DE, A, 3724190	1-3
T	Prostaglandins, vol. 11, No. 1, January 1976; W.L. MILLER et al.: "Relative biological activity of certain prostaglandins and their enantiomers", pages 77-84, see page 80, table 1	1-3

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 April 1992 (28.04.92)	24 June 1992 (24.06.92)
International Searching Authority	**Signature of Authorized Officer**
European Patent Office	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. DE 9100881 SA 53148

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 27/05/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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